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EXPERIMENTAL STUDIES

Inotropic Stimulation of Reperfused Myocardium With Dopamine: Effects on Infarct Size and Myocardial Function

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Prolonged postischemic ventricular dysfunction ("stunned myocardium") may be responsible for heart failure after myocardial reperfusion. Although inotropic stimulation can enhance the contractility of stunned myocardium, it could potentially increase infarct size and thereby impair ultimate recovery of myocardial function. In 16 anesthetized dogs, the left anterior descending coronary artery was occluded for 2 hours, and then reperfused. At 45 minutes of reperfusion, the dogs were randomized to receive a 3 hour intravenous infusion of either saline solution or dopamine (10 μg/kg per min), and 1 hour after the infusion was discontinued the area of necrosis and an in vivo area at risk of necrosis were determined. All dogs had serial two-dimensional echocardiograms with computer-assisted analysis and in vivo biopsies for determination of adenosine triphosphate and creatine phosphate levels.

Dopamine caused an increase in the contractility of the reperfused myocardium, with systolic wall thickening increasing from −4.1 ± 2.6 (mean ± SEM) to +24.0 ± 3.7% ($p < 0.002$) and short-axis cross-sectional ejection fraction increasing from 27.1 ± 4.7 to 71.6 ± 4.4% ($p < 0.002$) after 15 minutes of infusion. Regional myocardial blood flow in the previously ischemic epicardium was increased from 1.18 ± 0.11 ml/min per g with saline to 2.95 ± 0.36 ml/min per g with dopamine ($p < 0.03$). One hour after discontinuing the infusion, there were no significant differences between the dopamine-treated and saline-treated groups in the area of necrosis, expressed as a percent of the area at risk (31.1 ± 7.2% dopamine versus 35.8 ± 5.6% saline), in the systolic wall thickening (−9.5 ± 1.4% dopamine versus −10.4 ± 3.0% saline), or in the short-axis cross-sectional ejection fraction (10.0 ± 2.8% dopamine versus 15.1 ± 3.9% saline). Similarly, there were no differences between the two groups in either endocardial or epicardial adenosine triphosphate or creatine phosphate concentrations. Thus, prolonged inotropic stimulation with dopamine for 3 hours augmented contractility of reperfused canine myocardium, but did not cause a deterioration in myocardial function, a reduction of myocardial high energy phosphate stores or an increase in infarct size 1 hour after cessation of dopamine infusion.

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Reperfusion of ischemic myocardium, if initiated early after the ischemic insult, has been demonstrated to reduce infarct size (1–4). However, reperfusion does not benefit cardiac function immediately; instead, function improves gradually over days or even weeks (5–8). This prolonged, postischemic ventricular dysfunction has been termed "stunned myocardium" (9). It is now possible, in patients with acute myocardial infarction due to coronary thrombosis, to induce rapid thrombolysis in an occluded coronary artery with resultant reperfusion and salvage of jeopardized ischemic myocardium (10–14). Stunning of the myocardium is also observed in the clinical setting, because there is usually no immediate change in left ventricular function after thrombolysis, although improvement may be seen 1 to 3 weeks later (11,15).

Since failure of the myocardial pump with resultant pulmonary edema or cardiogenic shock is a major problem in patients hospitalized with acute myocardial infarction (16), some patients treated successfully with reperfusion of the occluded coronary artery will require positive inotropic support. Although inotropic agents may have a deleterious ef-

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fect on ischemic myocardium, extending the area of ischemic injury (17), they can increase the contractility of the stunned myocardium at least transiently (18,19). However, it is possible that with its attendant increase in myocardial oxygen demands, inotropic stimulation of myocardium displaying postischemic depression of left ventricular function could cause further ischemic damage of the salvaged myocardium, resulting in a further deterioration of function, depression of high energy phosphate stores and necrosis of the previously ischemic myocardium.

This study was designed to investigate the effects of a commonly used inotropic agent, dopamine, on reperfused canine myocardium. In particular, we studied the effect of dopamine on regional myocardial blood flow, high energy phosphate stores and myocardial function both during the infusion and during recovery 1 hour after infusion and on the ultimate size of the infarct.

Methods

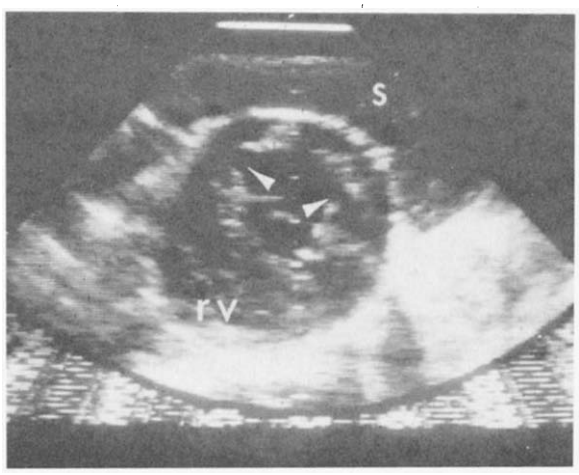
Animal preparation. Twenty-four mongrel dogs of either sex (weight 20 to 40 kg) were anesthetized with sodium pentobarbital (30 mg/kg body weight), intubated and ventilated with room air using a Harvard respirator. Additional sodium pentobarbital was administered, as required, throughout the remainder of the experiment to maintain adequate anesthesia. Cannulas were inserted into the left common carotid artery for continuous measurement of arterial pressure and withdrawal of blood samples during measurement of regional myocardial blood flow, and into the left jugular vein for administration of intravenous fluid and drugs. The chest was opened through a left thoracotomy and the heart exposed in a pericardial cradle. A cannula was inserted into the left atrium for the injection of microspheres to measure regional myocardial blood flow. A Millar micromanometer tip catheter, placed into the left ventricle through the left atrium, recorded left ventricular end-diastolic pressure. The left anterior descending coronary artery was isolated within 2 cm of its origin.

Animals used in this study were maintained in accordance with the guidelines of the Committee on Animals of the Harvard Medical School and those prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animals Resources, National Research Council (DHEW Publication No. [NIH] 78-23, revised 1978).

Protocol. After an intravenous bolus injection of lidocaine (1.5 mg/kg) the coronary artery was occluded for 2 hours using an atraumatic Schwartz vascular clamp. The clamp was then abruptly released, allowing reperfusion of the coronary vascular bed. After 45 minutes of reperfusion, the dogs were randomly allocated to receive a 3 hour intravenous infusion of either dopamine (10 μg/kg per min) or an equal volume (30.6 ml/h) of isotonic saline solution. One hour after this infusion was discontinued, the coronary artery was temporarily reoccluded and phthalo blue pigment (Dupont) (1 mg/kg) was injected into the left atrial cannula for determination of the in vivo area at risk of necrosis. The dogs then received additional pentobarbital and the heart was removed from the chest, dissected free of surrounding tissue and its surface sprayed with liquid Freon, which allowed even sectioning into 4 to 5 mm transverse slices. The area unstained by phthalo blue pigment was measured by planimetry, and represented the in vivo area at risk of necrosis. The slices were then incubated in triphenyltetrazolium chloride for 10 minutes and washed in formalin; all unstained areas were measured carefully by planimetry, and the value was considered to represent the area of necrosis (20). The heart slices were weighed, and approximately 1 g samples of myocardium were cut from the epicardial, mid and endocardial regions, in the center of the necrotic and nonischemic areas, for determination of regional myocardial blood flow.

Hemodynamics and myocardial blood flow. Heart rate, systolic and diastolic arterial pressures and left ventricular end-diastolic pressure were recorded at baseline (before injection of lidocaine), after 30 minutes of occlusion, after 20 minutes of reperfusion, after 15 minutes and 3 hours of infusion and 60 minutes after the infusion was stopped. Regional myocardial blood flow was determined at 25 minutes of reperfusion and at 60 minutes of infusion by the injection of radioactive microspheres (scandium-46, tin-113) as described by Domenech et al. (21).

Echocardiographic analysis. Two-dimensional echocardiograms were recorded at baseline (before injection of lidocaine), after 105 minutes of occlusion, after 20 minutes of reperfusion, after 15 minutes and 3 hours of infusion and 60 minutes after the infusion was stopped. The echocardiograms were obtained in the short-axis view, at the level of mid to lower papillary muscle, using an ATL model 850A scanner with a 3.0 MHz transducer. Images were recorded on JVC video cassettes using a Panasonic NC-8200 recorder. A saline-filled glove was placed on the surface of the heart to position the epicardium within the focal zone of the transducer (8). A typical echocardiogram recorded during occlusion, with computer analysis, is shown in Figure 1. Using stop-frame analysis, end-diastolic (onset of Q wave in lead II) and end-systolic (peak of T wave) epicardial and endocardial contours were traced onto acetate sheets and transferred by means of Summagraphics Super Grid System to a VAX computer with Tektronix 4014 terminal display. Four consecutive regular cardiac cycles were analyzed and averaged for each time point. End-systolic and end-diastolic wall thicknesses were determined at 2° intervals with a radial contraction model using the endocardial end-diastolic center of mass as the center point, and the epicardial center of mass and midseptal point to align the end-diastolic and end-systolic contours and to define the 0°



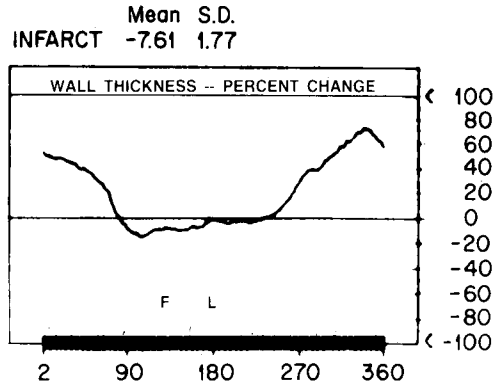


Figure 1. Two-dimensional echocardiogram in end-systole during coronary occlusion showing short-axis section at the level of the papillary muscles. The area which thins during systole is marked by **arrowheads.** Saline-filled glove (S) and right ventricle (rv) are indicated. Corresponding computer analysis of percent septal wall thinning for four consecutive cardiac cycles is shown below. Measurements begin at the midseptal point (0°). The central 45° of ischemia is marked between the first (F) and last (L) degrees of that octant, with the mean numerical value shown above.

reference point (8). The segment of myocardial wall that thinned during systole was calculated from the computer printout (Fig. 1). The central 45° of ischemia was calculated as the central 45° of the myocardial wall segment that exhibited systolic thinning during coronary occlusion.

Percent systolic wall thickening in the central 45° of ischemia was calculated as

$$\frac{(\text{End-systolic wall thickness} - \text{End-diastolic wall thickness}) \times 100}{\text{End-diastolic wall thickness}}.$$

Short-axis ejection fraction was calculated from the cross-sectional areas of the entire chamber as

$$\frac{(\text{End-diastolic area} - \text{End-systolic area}) \times 100}{\text{End-diastolic area}}.$$

Biochemical analysis. In vivo myocardial biopsy specimens were obtained at 30 minutes of reperfusion, 3 hours of infusion and 60 minutes after the infusion was stopped, from the center of the ischemic area and from nonischemic myocardium, using a disposable biopsy needle (Tru-Cut, Travenol). The specimens were rinsed immediately with iced saline solution, frozen within 5 seconds by immersion in liquid Freon, divided into endocardial and epicardial halves, and stored at −70°C until analysis. Adenosine triphosphate (ATP) and creatine phosphate were determined fluorimetrically (22) and are expressed as nanomoles per milligram cardiac protein.

Statistical analysis. Comparisons were performed between two means using Student's *t* test, and between multiple means using analysis of variance for repeated measurements. Bonferroni's correction was used to determine the level of statistical significance (23). All values are expressed as mean ± standard error of the mean.

Results

Three dogs died with ventricular fibrillation within 10 minutes of occluding the left anterior descending coronary artery. Two additional dogs died approximately 90 minutes after occlusion, and three dogs were excluded because of recurrent ventricular fibrillation during occlusion and reperfusion prior to randomization. Sixteen dogs completed the study, of which eight received dopamine and eight received saline infusion.

Hemodynamics (Fig. 2.). Dopamine significantly increased heart rate and systolic and diastolic arterial pressures throughout the infusion, but left ventricular end-diastolic pressure was elevated only at 15 minutes. The product of systolic pressure and heart rate (rate-pressure product) was increased from 18,750 ± 1,947 mm Hg · beats/min at 20 minutes reperfusion to 35,882 ± 2,471 mm Hg · beats/min at 15 minutes of dopamine infusion ($p < 0.002$). At 1 hour postinfusion, heart rate, blood pressure and the rate-pressure product were not different from values in the saline group.

Myocardial function (Table 1, Fig. 3). In the dogs that were to receive a saline infusion, short-axis cross-sectional ejection fraction during coronary occlusion decreased from 51.8 ± 2.9 to 10.3 ± 4.0% (Fig. 3A), with 181.0 ± 9.7° of the wall circumference thinned during systole (Fig. 3B); in the central 45° of ischemia, systolic wall thickening decreased from 38.2 ± 5.4 to −15.4 ± 1.3% (Fig. 3C). After 20 minutes of reperfusion, cross-sectional ejection fraction had increased to 31.4 ± 3.9%, wall thinning during systole had decreased to 68.5 ± 25.2° and systolic wall thickening in the central 45° of ischemia had increased to −0.6 ± 2.1%. There were no significant differences between these results and those for the dogs that were to receive a dopamine infusion. In the saline group, the early improvement in function at 20 minutes of reperfusion was

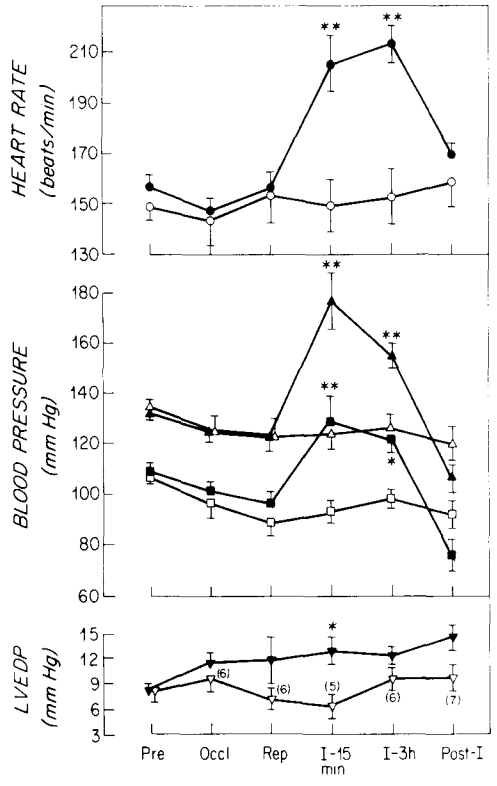


Figure 2. Heart rate, systolic (**triangles**) and diastolic (**squares**) blood pressures and left ventricular end-diastolic pressures (LVEDP) are shown during preocclusion (Pre) and at 30 minutes of occlusion (Occl), 20 minutes of reperfusion (Rep), 15 minutes and 3 hours of infusion (I-15 min, I-3h) and 1 hour postinfusion (Post-I). Saline-treated dogs are shown as **open symbols** and dopamine-treated dogs as **closed symbols**. Each point represents the mean of eight observations, except where otherwise indicated for left ventricular end-diastolic pressure with corresponding error bars. * $p < 0.05$ versus saline; ** $p < 0.001$ versus saline.

not sustained over 5 hours, with a decrease in cross-sectional ejection fraction to 15.1 ± 3.9%, an increase in degrees of systolic wall thinning to 128.3 ± 16.4° and a decrease in systolic wall thickening in the central 45° of ischemia to −10.4 ± 3.0%.

After 15 minutes of infusion, dopamine, compared with saline, had significantly increased cross-sectional ejection fraction to 71.6 ± 4.4% ($p < 0.002$) (Fig. 3A), with no segment of systolic wall thinning ($p < 0.002$) and an increase in systolic wall thickening in the central 45° of ischemia to 24.0 ± 3.7% ($p < 0.002$). At 3 hours, the changes induced by dopamine tended to be of lesser degree than those at 15 minutes, though values were still significantly greater than at preinfusion. One hour after dopamine was discontinued, function had declined to levels similar to those observed in the saline control group (Fig. 3).

Myocardial blood flow (Table 2). Regional myocardial blood flow showed some variability among individual dogs. However, there was no difference between the saline- and dopamine-treated groups in either the previously ischemic or nonischemic regions when the measurements were made at 25 minutes of reperfusion, that is, before dopamine infusion. After 1 hour of dopamine infusion, blood flow to the epicardial region of reperfused myocardium was significantly increased and there was an approximate doubling of blood flow to all regions in the nonischemic myocardium. Blood flow to the previously ischemic endocardium and midmyocardium was increased with dopamine, though this did not reach statistical significance, perhaps because of some vascular damage, as occurs with the "no-reflow" phenomenon (24), or because of an attenuated demand resulting from less viable contracting muscle in these regions.

Table 1. Echocardiographic Results for Percent Systolic Wall Thickness, Degrees of Systolic Wall Thinning and Short-Axis Cross-Sectional Ejection Fraction

	Systolic Wall Thickness (%)						Systolic Wall Thinning°						Short-Axis Cross-Sectional Ejection Fraction					
	Rep 20 min		I-15 min		Post-I		Rep 20 min		I-15 min		Post-I		Rep 20 min		I-15 min		Post-I	
	SAL	DA	SAL	DA	SAL	DA	SAL	DA	SAL	DA	SAL	DA	SAL	DA	SAL	DA	SAL	DA
	− 3.5	4.7	−11.4	14.0	−15.2	− 8.8	62	38	126	0	166	140	41	40	22	65	6	19
	8.6	−4.1	2.2	19.6	3.8	− 3.7	0	118	20	0	78	138	46	7	40	67	36	2
	− 5.3	3.4	− 4.9	27.4	1.6	−12.1	134	42	80	0	42	160	39	43	24	85	14	2
	− 3.9	−3.6	− 4.6	12.7	−11.2	−15.8	186	114	176	0	162	184	18	9	19	69	15	18
	2.6	6.1	− 8.3	45.3	−13.9	− 6.7	44	4	146	0	146	136	17	54	9	84	0	7
	4.0	3.6	1.7	21.5	−14.4	− 7.4	0	46	38	0	150	158	36	8	37	56	11	8
	−10.0	1.3	−14.3	30.0	−20.9	−13.4	122	26	154	0	168	118	22	32	18	88	16	21
	2.4	−5.9	6.8	21.4	−12.6	− 8.4	0	78	0	0	114	174	33	27	48	60	24	4
Mean	−0.6	0.7	−4.1	24.0	−10.4	−9.5	69	58	93	0	128	151	31	28	27	72	15	10
±SEM	2.1	1.6	2.6	3.7	3.0	1.4	25	15	24	0	16	8	4	6	5	4	4	3
p	NS		< 0.002		NS		NS		< 0.002		NS		NS		< 0.002		NS	

DA = dopamine; I-15 min = 15 minutes of infusion; Post-I = 1 hour postinfusion; Rep 20 min = 20 minutes of reperfusion; SAL = saline.

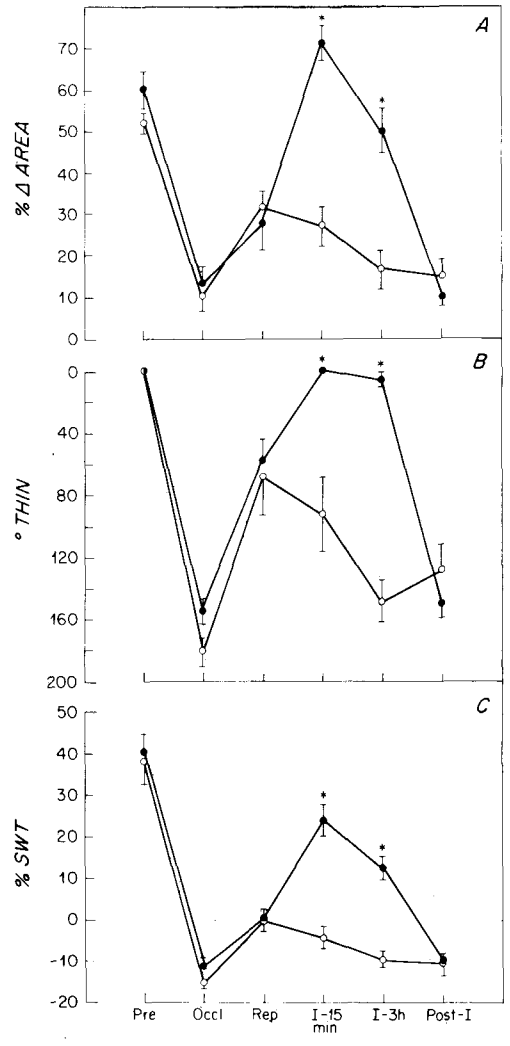


Figure 3. Myocardial function during preocclusion (Pre), and at 15 minutes before release of occlusion (Occl), 20 minutes of reperfusion (Rep), 15 minutes and 3 hours of infusion (I-15 min, I-3h) and 1 hour postinfusion (Post-I). **A**, Percent change in left ventricular short-axis cross-sectional area (%△ AREA); **B**, number of arc degrees of systolic wall thinning (°THIN); **C**, percent change in systolic wall thickening (%SWT) in central 45° of ischemic myocardium. ○ = saline treated; ● = dopamine-treated; * $p <$ 0.002 versus saline.

Area of necrosis (Table 3). There were no significant differences between the saline- and dopamine-treated groups in the area at risk of necrosis and in the area of necrosis expressed as a percent of either the total left ventricle or of the area at risk; the latter was 35.8 ± 5.6% in the saline-treated control dogs and 31.1 ± 7.2% in the dopamine-treated dogs.

High energy phosphates (Table 4). During reperfusion in the saline-treated group, ATP concentrations in the nonischemic endocardium and epicardium were 37.3 ± 1.3 and 35.4 ± 1.6 nmol/mg protein, respectively, but in the previously ischemic endocardium and epicardium the levels were reduced to 7.6 ± 2.0 and 14.5 ± 1.6 nmol/mg protein, respectively ($p < 0.002$). These levels did not recover significantly during or up to 1 hour after saline infusion. In the dopamine-treated group, ATP levels were not significantly different from those in the saline group during reperfusion or dopamine infusion or at 1 hour after cessation of the infusion.

In the saline group, creatine phosphate concentrations in the nonischemic endocardium and epicardium after 30 minutes of reperfusion were 50.1 ± 3.9 and 52.8 ± 3.9 nmol/mg protein, respectively. At this time, compared with myocardium that had never been ischemic, creatine phosphate levels in the previously ischemic myocardium were reduced in the endocardium (15.4 ± 2.5 nmol/mg protein, $p < 0.003$) but not in the epicardium (48.2 ± 8.1 nmol/mg protein, $p > 0.05$). One hour after cessation of the saline infusion, that is, after 4¾ hours of reperfusion, creatine phosphate levels in the endocardium had not changed significantly ($p = 0.22$) but had increased in the epicardium to 69.7 ± 9.4 nmol/mg protein ($p < 0.04$ versus 30 minutes of reperfusion). Individual variation was noted among the dogs. At 20 minutes of reperfusion creatine phosphate levels in the endocardium appeared lower in the saline group, while during infusion and at 1 hour postinfusion, these levels in both the endocardium and the epicardium appeared lower in the dopamine group. However, no significant differences were seen between the dopamine and the saline groups at any of the measured time points.

Table 2. Regional Myocardial Blood Flow (ml/min per g)

	Previously Ischemic				Nonischemic			
	SAL	DA		p	SAL	DA		p
Reperfusion								
Endo	1.98 ± 0.44	1.80 ± 0.36	(8)	NS	1.27 ± 0.22	1.67 ± 0.15	(8)	NS
Mid	1.52 ± 0.32	1.73 ± 0.17	(8)	NS	1.48 ± 0.18	1.66 ± 0.17	(8)	NS
Epi	1.31 ± 0.16	1.97 ± 0.28	(8)	NS	1.49 ± 0.26	1.81 ± 0.18	(8)	NS
Infusion								
Endo	1.28 ± 0.30	1.72 ± 0.40	(7)	NS	1.20 ± 0.14	3.40 ± 0.50	(7)	< 0.05
Mid	0.82 ± 0.17	1.88 ± 0.31	(7)	NS	1.40 ± 0.20	3.41 ± 0.42	(7)	< 0.008
Epi	1.18 ± 0.11	2.95 ± 0.36	(7)	< 0.03	1.34 ± 0.14	3.19 ± 0.49	(7)	NS

Results are given as mean ± SEM; number of observations in parentheses. Endo = endocardium; Epi = epicardium; Mid = midmyocardium; other abbreviations as in Table 1.

Table 3. Area at Risk of Necrosis and Area of Necrosis Expressed as a Percent of the Left Ventricle, and Area of Necrosis Expressed as a Percent of Area at Risk of Necrosis

	AR/LV (%)		AN/LV (%)		AN/AR (%)	
	SAL	DA	SAL	DA	SAL	DA
	18.6	30.4	7.3	17.3	39.4	57.1
	25.6	25.6	9.3	9.0	36.3	35.3
	32.4	25.0	15.5	4.3	47.7	17.1
	26.9	31.2	12.4	18.6	46.2	59.8
	23.0	22.0	4.9	0.9	21.1	4.2
	28.9	29.6	17.2	11.5	59.7	38.9
	29.5	26.7	7.2	6.7	24.3	24.9
	20.7	13.0	2.4	1.5	11.4	11.6
Mean	25.7	25.4	9.5	8.7	35.8	31.1
± SEM	1.7	2.1	1.8	2.4	5.6	7.2
p	NS		NS		NS	

AN = area of necrosis; AR = area at risk of necrosis; LV = left ventricle; other abbreviations as in Table 1.

Thus, 1 hour after cessation of the infusion, ATP and creatine phosphate levels of the reperfused myocardium were not reduced in the dopamine-treated group in either the endocardial half, which tended to contain necrotic myocardium, or the epicardial half, which tended to contain nonnecrotic myocardium and could respond to dopamine stimulation.

Discussion

The fate of ischemic myocardium is determined by the balance between myocardial oxygen supply and demand (25,26). While the oxygen supply remains reduced, there may be progressive cell death as a function of the duration of the ischemic insult (2,3). Although reestablishing myocardial oxygen supply by coronary reperfusion will reduce the extent of myocardial necrosis depending on the duration and severity of the ischemic insult (27), the recovery of myocardial function may be substantially delayed (8,11,28). Recent studies, however, have demonstrated that reperfused, poorly contracting myocardial cells will respond, at least briefly, to inotropic stimulation with dopamine (18,19), although it has not been determined whether continued stimulation will maintain contractility, deplete energy stores and accelerate necrosis of these previously ischemic poorly contracting myocytes. Some evidence suggests that 30 minute infusions of isoproterenol and dobutamine, when administered to previously ischemic reperfused myocardium in an isolated rat heart model (29), do not induce further tissue damage.

Effects of dopamine stimulation on reperfused ischemic myocardium. The results of the present study demonstrate that previously ischemic reperfused myocardium can be stimulated with intravenous dopamine to contract actively for up to 3 hours. Furthermore, 1 hour after cessation of the infusion, when compared with values in the saline-treated control group, the function of the reperfused myocardium was not depressed, there was no depletion of high energy phosphate stores, and the extent of myocardial necrosis was not increased. Therefore, while dopamine can stimulate the function of the stunned myocardium, this stimulation for 3 hours does not appear to be harmful. These findings are of

Table 4. Intramyocardial Adenosine Triphosphate and Creatine Phosphate Concentration (nmol/mg cardiac protein) in the Endocardium and Epicardium of Nonischemic Myocardium and in Previously Ischemic Myocardium at 30 Minutes of Reperfusion, 3 Hours of Infusion and 1 Hour Postinfusion

	Nonischemic		Reperfusion		Infusion		Postinfusion	
	Endo	Epi	Endo	Epi	Endo	Epi	Endo	Epi
ATP								
SAL	37.3 ± 1.3	35.4 ± 1.6	7.6 ± 2.0	14.5 ± 1.6	6.2 ± 2.1	16.1 ± 2.8	6.7 ± 1.7	16.2 ± 2.2
DA	34.0 ± 2.2	33.8 ± 1.7	8.7 ± 2.3	13.1 ± 3.1	5.5 ± 1.8	14.6 ± 2.7	6.7 ± 1.7	15.3 ± 3.0
CP								
SAL	50.1 ± 3.9	52.8 ± 3.9	15.4 ± 2.5	48.2 ± 8.1	33.7 ± 14.6	65.4 ± 8.8	37.0 ± 12.4	69.7 ± 9.4
DA	49.2 ± 3.7	55.3 ± 2.9	32.6 ± 6.1	37.6 ± 7.8	21.7 ± 6.9	46.8 ± 7.0	30.0 ± 8.3	51.7 ± 9.5

ATP = adenosine triphosphate; CP = creatine phosphate; other abbreviations as in Tables 1 and 2. There were no significant differences between saline and dopamine groups. Results are given as mean ± SEM.

clinical relevance because left ventricular failure in the post reperfusion state is not unusual, and there is reluctance to stimulate the contractility of the postischemic poorly contracting myocardium and thereby increase its oxygen demands.

The ability of intravenous dopamine to cause prolonged stimulation of the reperfused myocardium without an increase in infarct size or decrease in high energy phosphate stores suggests that the primary cause of postischemic ventricular dysfunction is not an autoregulatory mechanism of self-preservation, whereby the myocardium contracts weakly to preserve its limited energy stores. Furthermore, although the exact cause of postischemic ventricular dysfunction remains unclear, inotropic stimulation of poorly contracting reperfused myocardium does not appear to be analogous to "whipping a tired horse." Infarct size was not increased, and this was probably due to the administration of dopamine while the coronary bed was reperfused which allowed oxygen supply to be maintained in the endocardium and midmyocardium, and actually increased in the epicardium as a result of an increase in regional myocardial blood flow.

However, in view of its unique hemodynamic effects, it is not clear if these results with dopamine may be extrapolated to other inotropic agents. Dopamine, in addition to its positive inotropic properties, has positive chronotropic effects and differential regional vasodilator and vasoconstrictor actions (30–34). Other inotropic agents may produce a different spectrum of hemodynamic effects. The dose of dopamine administered in the present study was chosen because it is similar to doses that have previously been shown to be effective in stimulating the reperfused myocardium (18,19), and it is a dose frequently given in the clinical setting (35). It produced an approximate doubling of the rate-pressure product which, in addition to the marked increase in contractility (23,25) and small elevation in left ventricular end-diastolic pressure, would be expected to increase myocardial oxygen consumption substantially. However, coronary blood flow was increased in the epicardium, presumably to meet this increase in oxygen demand. This increase in blood flow to the previously ischemic endocardium and midmyocardium was not significant, but stimulation with dopamine did not increase systolic wall thickening in this area above preocclusion values, and perhaps for this reason there was no further reduction in high energy phosphate stores or increase in the area of necrosis.

Regional function. With reperfusion, there was an improvement in pump function as reflected by the increase in short-axis cross-sectional ejection fraction and systolic wall thickening and a reduction in the extent of myocardial wall that thinned during systolic contraction. In the saline control group, these improvements gradually diminished over the ensuing 4 hours. Other studies from our laboratory (19) have previously shown that in a similar canine model with a 2 hour coronary occlusion followed by reperfusion, there is a transient but minimal recovery at 1 hour of reperfusion, but this is diminished by 24 hours of reperfusion. After release of brief coronary occlusions (5 to 15 minutes) there is actually a period of exaggerated improvement (36), which may be due to a hyperemic response. The presence of a hyperemic response after release of the coronary occlusion was suggested in the present study when blood flow in the endocardium and midmyocardium in the saline group during reperfusion is compared with flow in nonischemic myocardium during reperfusion and previously ischemic tissue during infusion of saline solution (Table 1). However, the duration of the hyperemic response after a 2 hour occlusion and its possible contribution to the initial improvement are not known. One hour after cessation of the infusion there was no difference in pump function between the saline- and dopamine-treated groups. This not only implies that dopamine did no harm, but also suggests that, in this experimental model of reperfused myocardium, dopamine did not result in sustained benefit after cessation of infusion, which is not surprising in view of the short half-life of the drug. The measurement of short-axis cross-sectional ejection fraction was influenced by the section of wall that was not ischemic and could respond normally to dopamine infusion. The degrees of systolic wall thinning and the systolic wall thickening, however, reflect directly the area of myocardium that was ischemic and, on reperfusion, became "stunned." This may explain why systolic wall thickening did not reach preocclusion values at 15 minutes of the dopamine infusion, while cross-sectional ejection fraction exceeded preocclusion values.

Area at risk of necrosis and area of necrosis. A measure of the quantity of myocardium at risk of necrosis is important because there are differences among dogs in the distribution of coronary vessels and their collateral connections. Postmortem, in vitro perfusion with phthalo pigments or barium gels (3,37) demarcates the occluded bed size but does not make allowance for the blood flow contribution through collateral blood vessels and therefore overestimates the actual size of the area at risk of necrosis. In vivo injection of albumin microspheres (38) or phthalo blue pigment appears more physiologic, since these markers enter perfused areas of myocardium. In the present study, blue pigment was injected at the end of the experiment, 1 hour after termination of dopamine. At this time there was no hemodynamic evidence that the drug was still active and, therefore, it would not be expected to alter blood flow distribution in the myocardium. The risk zones obtained by injection of albumin microspheres at 15 minutes of coronary occlusion and by dye injection after 6 hours of occlusion are highly comparable when measured in a similar dog model in which no dopamine or reperfusion is present (39).

The measurement of area of necrosis by incubation in triphenyltetrazolium chloride has been established as a reliable method of detecting myocardial infarction, showing a strong correlation with histologically determined necrosis

(40,41). In the rat, triphenyltetrazolium chloride staining can detect infarction sometimes as early as 30 minutes post-occlusion, almost always at 1 hour and always at 3 hours (41). Triphenyltetrazolium chloride staining shows a close correlation with histologically determined infarct size and distinguished early irreversibly damaged cells as assessed by electron microscopy from normal cells (42). These findings in the rat are consistent with those in the dog model, in which a close relation between triphenyltetrazolium chloride staining and electron microscopy was demonstrated (40). When reperfusion is performed, triphenyltetrazolium chloride staining can demonstrate infarction after very brief occlusions (43), and it has been suggested that there is enhanced accuracy in reperfused tissue compared with non-perfused tissue (permanent occlusion), possibly as a result of substrate or enzyme washout from dead cells, or injury by the reflow process (44). The results in the present study showed that dopamine did not increase myocardial necrosis; this is consistent with the concurrent results of myocardial function and high energy phosphate content, neither of which was substantially worse than in the saline group.

Limitations. This study was performed in an anesthetized, open chest canine model, and extrapolations to the clinical management of patients should be made cautiously. In particular, this model allows complete reperfusion of the coronary artery, but in patients subjected to thrombolytic therapy alone, there is often a residual stenosis that may prevent the increase in myocardial blood flow seen in the epicardium of the previously ischemic zone during dopamine stimulation. However, this probably does not apply to patients in whom reperfusion is carried out by means of angioplasty or coronary bypass grafting (alone or after thrombolysis). The model also produces an abrupt, complete occlusion to previously healthy myocardium, whereas in patients there may be varying degrees of ischemia with previously damaged myocardium. Dopamine was infused for 3 hours, but longer periods of stimulation could have a different effect. Recovery from dopamine was assessed at 1 hour after cessation of the infusion, and although the effects of dopamine wear off very rapidly, it is possible that observation for a longer period of time might uncover subtle differences.

Conclusions. In this dog model, a 3 hour infusion of dopamine may be used to increase the contractility of reperfused myocardium without a resultant increase in infarct size, reduction in high energy phosphate stores or deterioration in myocardial function when measured 1 hour after cessation of the infusion. Therefore, short-term cautious administration of this agent may be considered in the treatment of severe cardiac failure during periods of postischemic ventricular dysfunction. It remains important to determine whether these conclusions apply in the presence of residual stenosis, to infusions of longer duration and to inotropic agents other than dopamine.

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